Collateral-based selection for endovascular treatment of acute ischaemic stroke in the late window (MR CLEAN-LATE): 2-year follow-up of a phase 3, multicentre, open-label, randomised controlled trial in the Netherlands

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Summary

Background The MR CLEAN-LATE trial provided evidence for the safety and efficacy of endovascular treatment for acute ischaemic stroke within the late window (after 6–24 h) in patients who were preselected based on the presence of collateral flow on CT angiography. We aimed to evaluate clinical outcomes 2 years after randomisation.

Methods MR CLEAN-LATE was a phase 3, multicentre, open-label, blinded-endpoint, randomised controlled trial conducted at 18 stroke intervention centres in the Netherlands. If endovascular treatment could be initiated within 6–24 h of symptom onset or last seen well, patients (aged 18 years or older) with an acute ischaemic stroke due to a large vessel occlusion in the anterior circulation and at least some collateral flow in the affected middle cerebral artery territory on CT angiography were randomly assigned (1:1) to either endovascular treatment with best medical treatment (endovascular treatment group) or best medical treatment alone (control group). Web-based randomisation, stratified by centre, was performed with the use of permuted blocks (block size eight to 20). The researchers who collected clinical outcomes and analysed the results were masked to treatment allocation; treating physicians, local investigators, and patients were aware of the received treatment. The primary outcome of MR CLEAN-LATE was the modified Rankin Scale (mRS) score at 90 days after randomisation. For this 2-year prespecified analysis, the primary outcome was mRS score at 2 years (minus 3 months to plus 6 months). Primary and safety analyses were performed based on the modified intention-to-treat principle, and included patients who provided (deferred) consent or died before consent could be obtained. Missing data were handled with multiple imputation by chained equations. The trial is completed and is registered at ISRCTN, ISRCTN19922220.

Findings Between Feb 2, 2018, and Jan 27, 2022, 535 patients were randomly assigned in the MR CLEAN-LATE trial, of whom 502 (94%) gave deferred consent and comprised the modified intention-to-treat population (255 in the endovascular treatment group and 247 in the control group). 261 (52%) patients were female and 241 (48%) were male. Data for mRS score at 2 years were available for 226 (89%) patients in the endovascular treatment group and for 202 (82%) patients in the control group. The median mRS score at 2 years was 4 (IQR 2–6) in the endovascular treatment group and 6 (2–6) in the control group. The endovascular treatment group demonstrated a shift towards better functional outcomes on the mRS (adjusted common odds ratio 1·41 [95% CI 1·00–1·99]; p=0·049). All-cause mortality at 2 years was 34% (87 of 255) in the endovascular treatment group and 41% (101 of 247) in the control group (adjusted hazard ratio 0·81 [95% CI 0·60–1·08]; p=0·15). Major vascular events (ie, transient ischaemic attack, ischaemic stroke, haemorrhagic stroke, and cardiac events) were reported between 90 days and 2 years in 23 patients in the endovascular treatment group and 13 patients in the control group.

Interpretation Our results show that the effectiveness of late-window (after 6–24 h) endovascular treatment in improving clinical outcomes is sustained for up to 2 years in a population preselected based on the presence of collateral flow on CT angiography. This finding might be important for prompting further evaluations of cost-effectiveness, health-care policy development, and clinical decision making.

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See Online for appendix

Research in context

Evidence before this study

PubMed was searched for randomised clinical trials reporting on long-term outcomes (≥1 year after randomisation) of late-window (6–24 h after symptom onset or last seen well) endovascular treatment from Jan 1, 2015, to March 30, 2024. The following keywords were used: ([{"ischemic stroke" AND "therapy/broad[filter]"} OR {"acute stroke" OR "cerebral ischemia" OR "cerebral infarction" OR "acute cerebral infarction" OR "brain embolism"}]) AND (["endovascular procedures" OR "endovascular procedure" OR "thrombectomy" OR "embolectomy" OR "thrombectomies" OR "embolectomies"]). No language restriction was applied. From the published studies on late-window endovascular treatment, only two trials reported long-term outcomes. The first trial examined 1-year outcomes from the REVASCAT trial, which included patients with small ischaemic cores (Alberta Stroke Program Early CT Score [ASPECTS] of >6) up to 8 h after symptom onset. The second trial investigated 1-year outcomes from the SELECT2 trial, which included patients with large-core ischaemic stroke (>50 mL or ASPECTS of 3–5) up to 24 h from symptom onset or last seen well. Both trials reported sustained improvements in functional outcomes 1 year after stroke. However, as the MR CLEAN-LATE trial used selection based on the presence of collateral flow on CT angiography in the 6–24 h time window, it remains unclear whether late-window endovascular treatment shows long-term effectiveness in this population as well.

Added value of this study

Our study is, to our knowledge, the first to show the effectiveness of collateral-based selection for late-window endovascular treatment of patients with ischaemic stroke up to 2 years after randomisation. As the selection criteria of the MR CLEAN-LATE trial were simple and pragmatic, these long-term follow-up results further underscore the value of late-window endovascular treatment for a large group of patients. Furthermore, as collateral-based selection with CT angiography is more widely available than perfusion imaging, these results promote the long-term effectiveness of late-window endovascular treatment in settings with limited access to perfusion imaging.

Implications of all the available evidence

Our results show that collateral-based selection for late-window endovascular treatment yields sustained patient benefits for up to 2 years after stroke. Combined with the results of previous published studies, this 2-year follow-up confirms that late-window endovascular treatment offers long-term gains in clinical outcomes in a broad patient population.

Introduction

The MR CLEAN-LATE trial showed the 90-day safety and efficacy of endovascular treatment within the late window (6–24 h after symptom onset or last seen well) for patients with acute ischaemic stroke in the anterior circulation due to large vessel occlusion in a population selected based on the presence of collateral flow on CT angiography.[1] These results provided evidence that patient selection in the late window could be primarily based on the presence of collateral flow and expanded treatment selection to a larger population. Although previous studies have shown the benefits of early-window endovascular treatment in reducing functional dependence up to 2 years after stroke,[2–4] it remains uncertain whether late-window endovascular treatment offers the same long-term benefits. Information on these long-term outcomes can be valuable for both clinical decision making and health-care policy development. In this prespecified follow-up to MR CLEAN-LATE, we aimed to assess the clinical outcomes of patients at 2 years after randomisation.

For the **statistical analysis plan** see https://www.contrast-consortium.nl/mr-clean-late-extended-follow-up/

Methods

Study design

MR CLEAN-LATE[1] was a phase 3, multicentre, open-label, randomised controlled trial with masked endpoint evaluation (PROBE design), conducted at 18 stroke intervention centres in the Netherlands. The central medical ethics committee at Erasmus MC, University Medical Center Rotterdam approved the trial (MEC-2017-367). This 2-year follow-up was prespecified in the study protocol.[5] The statistical analysis plan for the extended follow-up can be accessed online. The MR CLEAN-LATE trial was registered with the ISRCTN, ISRCTN19922220.

Participants

Detailed information on the trial design and proceedings, including all inclusion and exclusion criteria, have been described previously.[1,5] In brief, inclusion criteria were age 18 years or older, an acute ischaemic stroke due to a large vessel occlusion in the anterior circulation, the possibility of endovascular treatment initiation within 6–24 h of symptom onset or last seen well, and at least some collateral flow in the affected middle cerebral artery territory as observed on CT angiography. Patients meeting clinical and CT perfusion imaging criteria for late-window endovascular treatment outlined in the prevailing Dutch national guidelines, which were based on the DAWN[6] and DEFUSE-3[7] trials, were excluded from the study. These criteria comprised an occlusion of the internal carotid artery terminus or the first segment of the middle cerebral artery, a National Institutes of Health Stroke Scale (NIHSS) score of 10 or more, an ischaemic core of 25 mL or less, and a total ischaemic volume to ischaemic core ratio of 2 or more assessed on CT perfusion or magnetic resonance perfusion or diffusion.[1,6,7] Written

(deferred) informed consent for the trial proceedings was obtained from all patients or their representatives. Biological sex (male or female) data were derived from medical records.

Randomisation and masking

Patients were assessed for eligibility and enrolled in the trial by treating physicians. Included patients were randomly assigned (1:1) to undergo endovascular treatment with best medical treatment (endovascular treatment group) or best medical treatment alone (control group). Web-based randomisation, stratified by centre, was performed with the use of permuted blocks (block size of eight to 20). The researchers who collected 90-day, 1-year, and 2-year clinical outcomes, and analysed the results, were masked to treatment allocation. Treating physicians, local investigators, and patients were aware of the received treatment.

Procedures

Details on the intervention and 90-day data collection were described in the trial protocol and the 90-day outcome paper.[1,5] In the endovascular treatment group, the interventionist selected the device (stent-retriever or aspiration device), requiring that it was CE-marked. Stent placement with additional antiplatelet therapy was allowed if necessary. Best medical treatment could include admission to a stroke unit or intensive care unit, secondary prevention, and rehabilitation. Patients were included in the MR CLEAN-LATE trial from Feb 2, 2018, to Jan 27, 2022. On April 20, 2021, the extended follow-up procedures were added to the trial protocol. Follow-up assessments took place at 1 year (plus or minus 3 months) and at 2 years (minus 3 months to plus 6 months) after randomisation. A trained researcher from the coordinating centre conducted a telephone interview with the patient or their representative at each follow-up point. In the telephone interview, standardised forms were used to assess scores on the modified Rankin Scale (mRS), the five-level EQ-5D (EQ-5D-5L) health-related quality of life score, and the Barthel Index, and to collect information on the occurrence of major vascular events. If patients declined consent for the 2-year follow-up procedure, if patients were unreachable, or if the 2-year follow-up point had already passed at the start of the follow-up procedure, the Dutch Death Certificate Register was consulted to assess the vital status of the patient.

Outcomes

The primary outcome for this prespecified 2-year follow-up was the mRS score at 2 years after randomisation. The mRS is a 7-point scale for functional outcome and ranges from 0 (no symptoms) to 6 (death).[8] Secondary outcomes were the dichotomised mRS scores of 0–1 versus 2–6, 0–2 versus 3–6, and 0–3 versus 4–6 at 2 years; all-cause mortality during the 2-year follow-up; quality of life at 2 years using utility values derived from EQ-5D-5L responses using a Dutch value set with a theoretical range from –0·446 to 1·0 (full health);[9] interference with self-care activities according to the Barthel Index at 2 years, with scores ranging from 0 (severe disability) to 100 (no disability); and major vascular events between 90 days and 2 years after the index stroke, encompassing stroke (transient ischaemic attack, ischaemic stroke, or haemorrhagic stroke), major cardiac events, peripheral arterial disease, and thromboembolic events. Deceased patients received an EQ-5D-5L-derived utility value and Barthel Index score of 0.

	Endovascular treatment group (n=255)	Control group (n=247)
Age, years	74 (64–80)	74 (64–81)
Sex		
Female	148 (58%)	113 (46%)
Male	107 (42%)	134 (54%)
NIHSS score	10 (6–17)	10 (6–18)
Time from symptom onset or last seen well to random assignment, min	709 (542–910)	682 (532–887)
Time from symptom onset or last seen well to door of endovascular treatment centre, min	665 (485–862)	630 (478–851)
Treatment with intravenous thrombolysis	12 (5%)	19 (8%)
Witnessed stroke onset	35 (14%)	21 (9%)
Systolic blood pressure, mm Hg	155 (136–176)	154 (140–174)
Medical history		
Ischaemic stroke	51/254 (20%)	40/246 (16%)
Atrial fibrillation	51/254 (20%)	53/246 (22%)
Diabetes	35/254 (14%)	39/246 (16%)
Hypertension	142/254 (56%)	118/245 (48%)
mRS score before stroke		
0	145/254 (57%)	159/247 (64%)
1	66/254 (26%)	47/247 (19%)
2	38/254 (15%)	36/247 (15%)
3 or 4	5/254 (2%)	5/247 (2%)
Proximal target occlusion		
Internal carotid artery	5/255 (2%)	7/247 (3%)
Internal carotid artery terminus	32/255 (13%)	32/247 (13%)
M1	135/255 (53%)	126/247 (51%)
M2	80/255 (31%)	76/247 (31%)
Other or none	3/255 (1%)	6/247 (2%)
Tandem lesion	51/248 (21%)	57/236 (24%)
ASPECTS	9 (7–10)	8 (7–9)
Collateral grade		
0 (absent collateral filling)	11/251 (4%)	15/246 (6%)
1 (filling ≤50%, but >0%)	67/251 (27%)	73/246 (30%)
2 (filling >50% but <100%)	109/251 (43%)	96/246 (39%)
3 (filling 100%)	64/251 (25%)	62/246 (25%)

Data are n (%), median (IQR), or n/N (%). Biological sex data (male or female) were derived from medical records. ASPECTS=Alberta Stroke Programme Early CT score. M1=first segment of middle cerebral artery. M2=second segment of middle cerebral artery. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale.

Table 1: **Baseline characteristics**

Statistical analysis

In the MR CLEAN-LATE trial,[1] a sample size of 500 patients (after covariate adjustments) was deemed to be sufficient to provide 84% power to detect a treatment effect on the mRS at 90 days in case of a common odds ratio (cOR) of 1·52 (two-sided α of 0·05). For this 2-year follow-up, a prespecified statistical analysis plan was followed. Analyses were performed in accordance with the modified intention-to-treat principle, including patients who provided (deferred) consent or died before consent could be obtained.

The primary outcome analysis examined the shift towards better functional outcome on the mRS at 2 years for endovascular treatment plus best medical treatment compared with best medical treatment alone. Ordinal logistic regression was used to estimate a cOR. For the secondary analyses of good versus poor outcome with dichotomised mRS scores, binary logistic regression was used. All-cause mortality was evaluated using the Kaplan–Meier method and using Cox regression. The records of patients in whom the vital status at 2 years was missing (due to an inability to consult the Dutch Death Certificate Register because of moving abroad) were censored at the last moment of follow-up. Linear regression models were used to estimate between-group differences in EQ-5D-5L-based utility scores and scores on the Barthel Index. In accordance with the analyses of 90-day outcomes, effect estimates from regression analyses were adjusted for age, mRS score before stroke, time from symptom onset or last seen well to randomisation, baseline NIHSS score, collateral grade, and unwitnessed stroke onset. For the analysis of major vascular events, person-years at risk were calculated to determine allocation-specific event rates and the rate ratio, which shows the event rate in the endovascular treatment group compared with the control group. If patients had multiple major vascular events during follow-up, all events were reported in the descriptive tables, and the time to the first event was used for statistical analyses. Appropriate assumptions were checked for all statistical analyses.

Predefined subgroup analyses were performed to assess the effect of age, sex, systolic blood pressure, baseline NIHSS score, time from symptom onset or last seen well to randomisation, time from symptom onset or first symptoms to randomisation, history of diabetes, history of atrial fibrillation, tandem lesion, occlusion location, Alberta Stroke Program Early CT Score, collateral flow, unwitnessed stroke onset, and intravenous thrombolysis on the treatment effect of endovascular treatment on the mRS.

Two sensitivity analyses were performed for mRS scores, dichotomised mRS scores, EQ-5D-5L-based utility scores, the score on the Barthel Index, and all-cause mortality. The first sensitivity analysis used an as-treated approach, with the definition of treated comprising patients who underwent groin puncture for endovascular treatment. The second sensitivity analysis included only patients with observed outcomes 2 years after randomisation (complete-case analysis).

All effect estimates are reported with their corresponding 95% CIs. p values of less than 0·05 were considered significant. For subgroup and secondary analyses, no correction for multiplicity was applied. Missing data were handled with multiple imputation by chained equations using mice version 3.16.0.[10] The required number of imputations was based on the fraction of missing information.[11] All regression analyses were conducted with imputed data. Additional details regarding imputation methods are in the appendix (p 2). Analyses were performed using R version 4.3.2.[12]

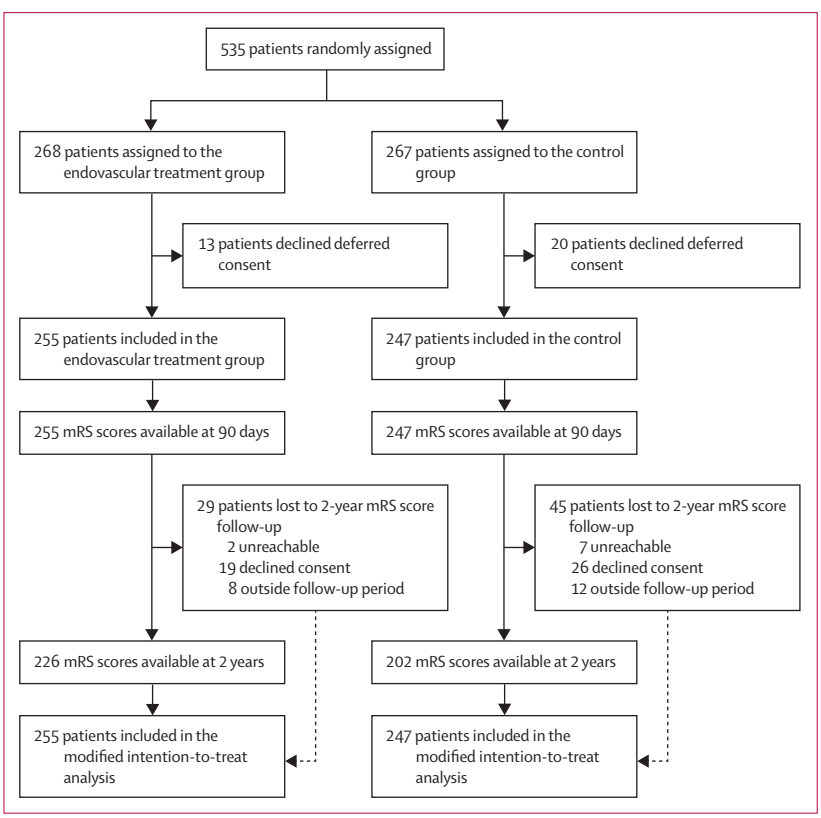
535 patients randomly assigned
268 patients assigned to the endovascular treatment group
267 patients assigned to the control group
13 patients declined deferred consent
20 patients declined deferred consent
255 patients included in the endovascular treatment group
247 patients included in the control group
255 mRS scores available at 90 days
247 mRS scores available at 90 days
29 patients lost to 2-year mRS score follow-up
2 unreachable
19 declined consent
8 outside follow-up period
45 patients lost to 2-year mRS score follow-up
7 unreachable
26 declined consent
12 outside follow-up period
226 mRS scores available at 2 years
202 mRS scores available at 2 years
255 patients included in the modified intention-to-treat analysis
247 patients included in the modified intention-to-treat analysis

Figure 1: **Trial profile**
mRS=modified Rankin Scale.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Feb 2, 2018, to Jan 27, 2022, 535 patients were randomly assigned in the MR CLEAN-LATE trial. 502 (94%) patients gave (deferred) consent and comprised the modified intention-to-treat population. 255 (51%) patients were allocated to the endovascular treatment group, and 247 (49%) patients were allocated to the control

	Endovascular treatment group (n=255)	Control group (n=247)	Measure of effect	Unadjusted value (95% CI)	Adjusted value* (95% CI)	p value
Primary outcome						
mRS score at 2 years†	4 (2–6)	6 (2–6)	cOR	1·32 (0·96 to 1·81)	1·41 (1·00 to 1·99)	0·049
Secondary outcomes						
Dichotomised mRS score of 0–1 *vs* 2–6 at 2 years†	40 (18%)	34 (17%)	OR	1·07 (0·67 to 1·72)	1·16 (0·69 to 1·95)	0·58
Dichotomised mRS score of 0–2 *vs* 3–6 at 2 years†	78 (35%)	55 (27%)	OR	1·37 (0·93 to 2·02)	1·79 (1·11 to 2·91)	0·018
Dichotomised mRS score of 0–3 *vs* 4–6 at 2 years†	110 (49%)	79 (39%)	OR	1·36 (0·95 to 1·95)	1·62 (1·04 to 2·52)	0·034
EQ-5D-5L score utility value at 2 years‡	0·40 (0·42)	0·34 (0·41)	β coefficient	0·06 (–0·02 to 0·13)	0·06 (–0·01 to 0·12)	0·079
Barthel Index score at 2 years§	53 (47)	42 (46)	β coefficient	7·45 (–0·67 to 15·57)	7·20 (0·51 to 13·88)	0·035
Mortality at 2 years¶	87 (34%)	101 (41%)	HR	0·81 (0·61 to 1·08)	0·81 (0·60 to 1·08)	0·15

Data are median (IQR), n (%), or mean (SD), except where otherwise stated. n (%) reported for dichotomised mRS scores are for better functional outcomes. Regression analyses were conducted after multiple imputation of missing data. p values are reported for adjusted analyses. cOR=common odds ratio. EQ-5D-5L=five-level EQ-5D. HR=hazard ratio. OR=odds ratio. mRS=modified Rankin Scale. *Adjustments were made for age, mRS score before stroke, time from symptom onset or last seen well to random assignment, baseline National Institutes of Health Stroke Scale NIHSS score, collateral grade, and unwitnessed stroke onset. †The mRS score was missing for 29 patients in the endovascular treatment group and 45 patients in the control group. ‡The EQ-5D-5L score utility value was missing for 30 patients in the endovascular treatment group and 46 patients in the control group. §The score on the Barthel Index was missing for 32 patients in the endovascular treatment group and 49 patients in the control group. ¶Vital status at 2 years was missing for two patients in the endovascular treatment group and one patient in the control group.

***Table 2*: Primary and secondary outcomes 2 years after random assignment in the modified intention-to-treat population**

group. The baseline demographic and clinical characteristics of the two trial groups were well balanced (table 1). 261 (52%) patients were female and 241 (48%) were male. Data for mRS score at 2 years were available for 226 (89%) patients in the endovascular treatment group and for 202 (82%) patients in the control group (figure 1). mRS scores for 20 (4%) patients were missing because the 2-year follow-up point had already passed at the start of the extended follow-up procedure; mRS scores for 54 (11%) patients were missing due to declined consent or an inability to reach the patient or proxy. Vital status at 2 years after stroke was available for 499 (99%) patients (missing for two patients in the endovascular treatment group and one patient in the control group).

At 2 years, the median mRS score was 4 (IQR 2–6) in the endovascular treatment group and 6 (2–6) in the control group (adjusted cOR 1·41 [95% CI 1·00–1·99]; p=0·049; table 2), indicating a shift in the distribution of mRS scores in favour of the intervention group. Patients allocated to the endovascular treatment group had significantly higher odds of good functional outcome (dichotomised mRS scores 0–2 *vs* 3–6, and 0–3 *vs* 4–6) compared with the control group, but there was no significant difference in excellent functional outcome (dichotomised mRS scores 0–1 *vs* 2–6) between the endovascular treatment group and the control group (table 2). All-cause mortality during the 2-year follow-up was reported for 87 (34%) of 255 patients in the endovascular treatment group and for 101 (41%) of 247 patients in the control group, but this difference was not significant (table 2, figure 2).

Quality of life assessed by the EQ-5D-5L score utility value was not significantly different between the two groups (table 2). The distribution of scores on each of the EQ-5D-5L dimensions is described in the appendix (p 3). Scores on the Barthel Index were significantly higher in patients in the endovascular treatment group than in the control group, indicating a better ability to perform activities of daily living (table 2).

Major vascular events from 90 days to 2 years after randomisation were reported in 23 patients in the endovascular treatment group (268 person-years, annual risk 8·6%) and in 13 patients in the control group (196 person years, annual risk 6·6%; rate ratio 1·30 [95% CI 0·63–2·79]; p=0·57). Recurrent stroke was the most often recorded major vascular event (table 3).

In the subgroup analyses of mRS score at 2 years, point estimates generally favoured endovascular treatment

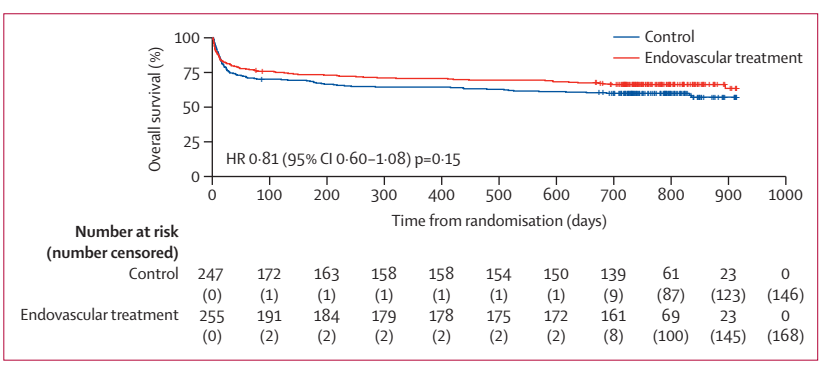

***Figure 2*: Kaplan–Meier plot of overall survival in the endovascular treatment group and control group during the 2-year follow-up**

Censored patients are indicated with vertical tick-marks. Three patient records were censored at the 90-day follow-up point due to an inability to assess vital status afterwards (due to living abroad and an inability to reach the patient or representative).

(appendix p 4), with significant interactions found between treatment effect and sex ($p_{interaction}$=0·043, treatment effect favours male sex), tandem lesions ($p_{interaction}$=0·019, treatment effect favours tandem lesion), and occlusion location ($p_{interaction}$=0·0029, treatment effect disfavours occlusions in the second and third segment of the middle cerebral artery). The sensitivity analyses showed similar treatment effects on the mRS score at 2 years (as-treated: adjusted cOR 1·44 [95% CI 1·02–2·03]; p=0·038; complete-case analysis: adjusted cOR 1·49 [1·02–2·17]; p=0·040) and the secondary outcome measures (appendix pp 5–6). The observed mRS scores (complete-case analysis) in the endovascular treatment and control groups at 2 years are shown in figure 3.

Discussion

In this prespecified extended follow-up of the MR CLEAN-LATE trial, we show that the beneficial effects of late-window (ie, after 6–24 h) endovascular treatment on clinical outcomes in a population with stroke, who were preselected on the presence of collateral flow on CT angiography are sustained for up to 2 years after randomisation. Patients in the endovascular treatment group showed a shift towards better functional outcomes on the mRS compared with the control group, and they had a higher likelihood of gaining functional independence. In addition to functional outcomes, late-window endovascular treatment led to a better performance in activities of daily living (as shown by higher scores on the Barthel index). Compared with the control group, quality of life (as assessed by EQ-5D-5L-based utility values) was improved in the endovascular treatment group, and mortality was lower, although these differences were not statistically significant.

Compared with the 90-day effect estimate for a shift towards better outcomes on the mRS (adjusted cOR 1·67 [95% CI 1·20–2·32]),[1] the 2-year effect estimate was lower. This difference might be explained by a worsening of functional outcome in the trial population through non-stroke related factors, as well as an increase in mortality.[13] Our findings on dichotomised mRS scores remain similar in magnitude to the 90-day effect estimates, suggesting a sustained higher probability of good functional outcome after endovascular treatment. The effect on EQ-5D-5L utility values and Barthel Index scores were likewise similar to the 90-day outcomes. Although long-term outcomes of comparable late-window endovascular treatment trials are currently not available, our findings align with the long-term follow-up results from early-window trials,[2–4] and the 1-year follow-up from the late-window SELECT2 trial (which included patients with a large ischaemic core on CT, CT perfusion, or MRI).[14]

In terms of safety, we did not find any long-term risks associated with late-window endovascular treatment. Cumulative mortality rates were non-significantly lower in the endovascular treatment group compared with the control group at 2 years after randomisation (87 [34%] *vs* 101 [41%]), and mortality increased proportionally in both treatment groups compared with the 90-day mortality rates (endovascular treatment 62 [24%] of 255, control 74 [30%] of 247).[1] The percentage point increase in mortality between the 90-day and 2-year follow-up was consistent with the previously reported results from the MR CLEAN trial.[3,15] Despite a higher occurrence of major vascular events in the endovascular treatment group than in the control group, these events were spread over more person-years in the endovascular treatment group and the rate ratio was not significant. The rates of recurrent ischaemic stroke or transient ischaemic attack in the endovascular treatment group (n=17 in 268 person-years, 6·3% annual risk) and control group (n=9 in 196 person-years, 4·6% annual risk) over a 2-year period do not seem disproportionate compared with previous studies,[16–18] in which a 4% 1-year recurrence

	Endovascular treatment group	Control group
Stroke events		
Transient ischaemic attack	6	2
Ischaemic stroke	11	7
Haemorrhagic stroke	1	1
Cardiac events		
Unstable angina pectoris	1	0
Myocardial infarction	0	1
Resuscitation	1	0
Other*	3	2
Total	23	13
Person years at risk	268	196
Annual risk of major vascular event	8·6%	6·6%

The 23 events in the intervention group occurred in 20 different patients. One patient had two transient ischaemic attacks and one ischaemic stroke, and another patient had a transient ischaemic attack and an ischaemic stroke. All events in the control group occurred in different patients. No events related to peripheral arterial disease or other thrombo-embolic events were observed. The annual risk was calculated by dividing the number of events by the person-years at risk. *Other cardiac events included cardioversion, implantation of pacemaker or defibrillator, heart failure, or life-threatening arrhythmia.

Table 3: **Major vascular events in the intervention and control groups between 90 days and 2 years after random assignment**

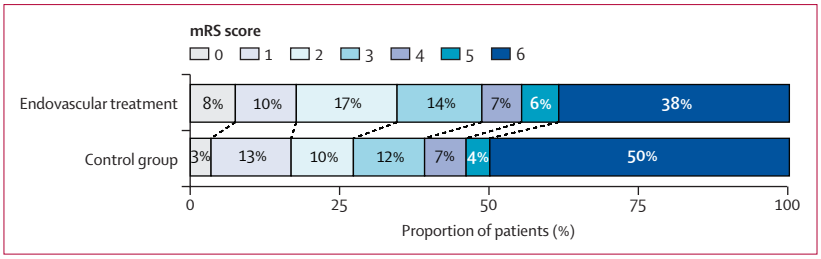

Figure 3: **Distribution of observed mRS scores**

Proportions were based on the total number of patients with observed mRS scores (complete cases) at 2 years after randomisation. The mRS score was missing for 29 (11%) of 255 patients in the endovascular treatment group and for 45 (18%) of 247 patients in the control group. mRS=modified Rankin Scale.

risk and an 11% 10-year recurrence risk have been reported. However, it is important to note that our follow-up period coincided with the COVID-19 pandemic; the effect of COVID-19 on mortality and the occurrence of major vascular events in our study is uncertain.[19]

The results of the subgroup analyses of the primary outcome were generally similar to those observed at 90 days. We noted a significant interaction between treatment effect and sex at 2 years after randomisation, which might suggest poorer treatment benefit for female patients ($p_{interaction}$=0·043). This interaction was also evident at 90 days, although it was not significant ($p_{interaction}$=0·11).[1] However, due to small sample sizes within subgroups and the absence of adjustments for multiplicity, caution should be made when interpreting the results of the subgroup analyses.

From a broader perspective, our study results might be important for prompting and supporting further evaluations of the cost-effectiveness of late-window endovascular treatment. Our findings highlight a sustained and clinically meaningful improvement in the likelihood of favourable functional outcomes during a 2-year follow-up period. A strength of this study is that we were able to complete the 2-year follow-up in a large number of patients, resulting in 85% availability of primary outcome data and 99% availability of vital status. Although previous trials have reported higher follow-up rates of the primary outcome (99% and 93%), those follow-up periods were confined to 1 year.[2,14] Our 2-year follow-up proceedings also commenced 3 years after the first patient inclusion. The as-treated and complete-cases analyses produced similar effect estimates, affirming the validity of our primary analysis. Nevertheless, this study has several limitations. First, the effect of the COVID-19 pandemic on our outcomes is uncertain. Second, mRS scores were more often missing in the control group than in the endovascular treatment group. The reduced reachability of patients in the control group could be due to more unfavourable outcomes, potentially introducing bias. Also, as the trial was exclusively conducted in the Netherlands, where high standards of secondary prevention and ongoing care are expected, the generalisability of long-term outcomes to other settings is uncertain. Last, because 89% of patients in the trial had an unwitnessed stroke, the time from stroke onset to endovascular treatment could have been short, possibly leading to similar long-term outcomes as observed in the early-window MR CLEAN trial. Although subgroup analyses at both 90 days and 2 years did not indicate any relationship between functional outcomes and whether the stroke was witnessed or not,[1] caution should be exercised when interpreting the results of subgroup analyses.

In conclusion, this study shows that the effectiveness of late-window endovascular treatment for acute ischaemic stroke in the anterior circulation caused by large vessel occlusion, in a population preselected based on collateral flow on CT angiography, is sustained for up to 2 years after stroke.

Contributors

Baseline data were collected by the MR CLEAN-LATE investigators as specified in the MR CLEAN-LATE study.[1] IH and FMEP collected the follow-up data beyond 90 days. IH, FMEP, WHvZ, RJvO, and SMJvK wrote the statistical analysis plan. IH, FMEP, and SMJvK performed the statistical analyses. IH and FMEP accessed and verified the underlying data reported in the manuscript. IH and FMEP wrote the first draft with input from RJvO, WHvZ, and SGHO. All authors contributed to manuscript writing and critical reviewing of the manuscript and had full access to all the study data. All authors had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

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Data sharing

Collected data, including de-identified participant data and a data dictionary defining each field in the set, will be made available on reasonable request. Requests can be made by submitting a proposal via email to the corresponding author.

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References

1 Olthuis SGH, Pirson FAV, Pinckaers FME, et al. Endovascular treatment versus no endovascular treatment after 6-24 h in patients with ischaemic stroke and collateral flow on CT angiography (MR CLEAN-LATE) in the Netherlands: a multicentre, open-label, blinded-endpoint, randomised, controlled, phase 3 trial. *Lancet* 2023; **401:** 1371–80.

2 Dávalos A, Cobo E, Molina CA, et al. Safety and efficacy of thrombectomy in acute ischaemic stroke (REVASCAT): 1-year follow-up of a randomised open-label trial. *Lancet Neurol* 2017; **16:** 369–76.

3 van den Berg LA, Dijkgraaf MGW, Berkhemer OA, et al. Two-year outcome after endovascular treatment for acute ischemic stroke. *N Engl J Med* 2017; **376:** 1341–49.

4 Palesch YY, Yeatts SD, Tomsick TA, et al. Twelve-month clinical and quality-of-life outcomes in the Interventional Management of Stroke III trial. *Stroke* 2015; **46:** 1321–27.

5 Pirson FAVA, Hinsenveld WH, Goldhoorn RB, et al. MR CLEAN-LATE, a multicenter randomized clinical trial of endovascular treatment of acute ischemic stroke in the Netherlands for late arrivals: study protocol for a randomized controlled trial. *Trials* 2021; **22:** 160.

6 Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018; **378:** 11–21.

7 Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018; **378:** 708–18.

8 van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; **19:** 604–07.

9 Versteeght MM, Vermeulen KM, Evers SMAA, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. *Value Health* 2016; **19:** 343–52.

10 van Buuren S, Groothuis-Oudshoorn K. MICE: multivariate imputation by chained equations in R. *J Stat Softw* 2011; **45:** 1–67.

11 Von Hippel PT. How many imputations do you need? A two-stage calculation using a quadratic rule. *Sociol Methods Res* 2020; **49:** 699–718.

12 R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing, 2024. https://www.R-project.org/ (accessed Jan 31, 2024).

13 Ganesh A, Luengo-Fernández R, Wharton RM, Rothwell PM. Ordinal *vs* dichotomous analyses of modified Rankin Scale, 5-year outcome, and cost of stroke. *Neurology* 2018; **91:** e1951–60.

14 Sarraj A, Abraham MG, Hassan AE, et al. Endovascular thrombectomy plus medical care versus medical care alone for large ischaemic stroke: 1-year outcomes of the SELECT2 trial. *Lancet* 2024; **403:** 731–40.

15 Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015; **372:** 11–20.

16 Berghout BP, Bos D, Koudstaal PJ, Ikram MA, Ikram MK. Risk of recurrent stroke in Rotterdam between 1990 and 2020: a population-based cohort study. *Lancet Reg Health Eur* 2023; **30:** 100651.

17 Amarenco P, Lavallée PC, Monteiro Tavares L, et al. Five-year risk of stroke after TIA or minor ischemic stroke. *N Engl J Med* 2018; **378:** 2182–90.

18 Flach C, Muruet W, Wolfe CDA, Bhalla A, Douiri A. Risk and secondary prevention of stroke recurrence: a population-base cohort study. *Stroke* 2020; **51:** 2435–44.

19 Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. *EClinicalMedicine* 2020; **29:** 100639.